

## REMARKS

Claims 1, 14-16, 19 and 21-30, 32, 33, and 37-44 are in the case. Claims 14-16, 19, 21-30, 32, 33 and 37-44 were rejected in this Office Action under 35 U.S.C. § 112, first paragraph. Claims 19, 21-30, 32 and 33 were rejected in this Office Action under 35 U.S.C. § 112, second paragraph as being indefinite. The Examiner has maintained certain rejections under 35 U.S.C. §112, second paragraphs from the previous Office Action.

Claims 1 and 14 were rejected under 35 U.S.C. §102(b,e) as being anticipated by Metzger et al. U.S. Patent No. 5,700,910 (Metzger). Claims 1, 14-16, 19, 21-30, 32, 33, and 37-44 were rejected under 35 U.S.C. §102 (b) as being anticipated by or in the alternative under §103 as being obvious over van Atta et al. US Patent No. 5,478,729 (Van Atta). Claim 1, 14-16, 19, 21-30, 32, 33, and 37-44 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of Van Atta.

Applicants believe that the amendments to and remarks regarding the claims overcome the rejections. Amendments to the claims are fully supported in the Specification. The description of the alkylating reagent having haloaldehyde or haloketone functional groups are found, for example, on page 2, lines 1-7, page 3, lines 3-9, and on page 17, line 15-18. The term that states that the haloaldehyde or haloketone group is derivatized with a protected functional group is supported in the specification, for example, in the reaction scheme shown on page 8 and at page 10, lines 4-8. While the specification does not recite the word "derivatized",

Applicants submit that the reaction scheme and the word "conversion" provide adequate support. Protecting groups are supported, for example, at page 2, lines 23-29 and page 3, lines 15-23.

#### Restriction Requirement

Applicants note that the Examiner in the restriction requirement has noted that BABA is the elected species for the restriction requirement. Applicants point out that BABA is the alkylating agent with which "protected" BABA is formed. BABA is not a "protected alkylating reagent". It is unprotected.

#### §112, First Paragraph Rejection

The Examiner rejected claims 14-16, 19, 21-30, 32, 33 and 37-44 "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claim invention (NEW MATTER REJECTION). As an example, the Examiner points to claim 1 (a claim that was not rejected under this paragraph) stating that the "protection and deprotection language" which was not present in the specification or original claims and to which no specification support was pointed to "constitutes new matter".

Applicants respectfully traverse the rejection. Applicants point out that claim 1, as originally filed, stated "a protected alkylating agent" and also stated that "deprotection" was by an enzyme. In fact, the entire specification discusses "protecting" alkylating agents and

"deprotecting" the "protected" alkylating agent by action of a catalyst or enzyme. On page 1, the specification discusses the benefits of alkylating agent, but states that the alkylating agents are problematic. Generally they are too reactive. See page 1, lines 1-22. The specification at page 2, lines 17-26 describes using protecting groups to permit long-term storage. Several protecting groups are listed. The specification discusses "deprotecting" the "protected alkylating agent". At page 2, line 23 the specification states that "deprotection" is catalyzed by an enzyme and at page 4, lines 9-11 states that an activating agent is an agent that is capable of deprotecting the protected alkylating agent. Preferred activating agents such as enzymes are listed throughout the specification.

In addition, the Examiner states that, for example, claim 19 was amended to include modification beyond conjugation with homocysteine. Applicants do not agree that claim 19 was so amended. Claim 19 was amended in the response dated October 2, 2001 to clarify what the protected functional group was and with what it reacts. Claim 19 as amended recited "capable of reacting with a nucleophilic group of **homocysteine**" vs. as filed which recited "capable of chemically modifying homocysteine". Applicants do not agree that the amendments to claim 19 and other claims that specifically recite homocysteine include modifications beyond conjugation with homocysteine.

Applicants respectfully submit that the amendments are supported in the specification request that the rejections be withdrawn.

§112, Second Paragraph Rejections- New

The Examiner rejected claims 19, 21-30, 32, 33, and 37-44 as being indefinite. The Examiner states that the term "*capable of reacting with a functional nucleophilic group*" and "*unreactive to a nucleophilic group*" are relative terms which render the claims indefinite.

Applicants respectfully traverse the rejection. While some of these terms have been amended, Applicants submit that the terms are definite within the requirements of the statute. One skilled in the art would understand these terms when reading the terms in light of the claim and the specification. In addition, as an example of similar terms that were found to be definite, the term "incapable of forming a dye with said oxidizing developing agent" was held to be perfectly acceptable by the courts. See, *In re Barr*, 444 F.2d 588 (CCPA 1971).

Thus, Applicants submit that the rejection should be withdrawn.

§112, Second Paragraph Rejections - Outstanding

The Examiner maintained the rejection of claims 1, 19, 32 and 44 on the basis that the term "protected alkylating agent" is indefinite as to what portion of the alkylating agent is "protected". Applicants submit that the amendments overcome the rejection. The halo ketone or halo aldehyde group is protected and this is set forth in the claims.

The Examiner maintained the rejection of claims 19, 32 and 44 stating that "chemically modifying homocysteine" or Homocysteine is modified by a reagent" lacks metes and bounds regarding the type of homocysteine modifications within the scope of the claim and the resulting homocysteine

structure. Claims 32 and 44 already recited that the reaction occurs at the sulfhydryl group of homocysteine and claim 19 has been so amended. Applicants submit that the claims are clear and definite as to the type of homocysteine modification and the resulting homocysteine structure. Thus, Applicants respectfully request that the rejection be withdrawn.

§102(b,e) Rejections under Metzger

Claims 1 and 14 were rejected as being anticipated by Metzger. With respect to claim 1, the Examiner states that Metzger discloses a "protected alkylating agent" of formula III (col. 2, line 45) and with respect to claim 14, that Metzger also discloses a "disulfide reducing agent" (e.g. ZN in HCL/H<sub>2</sub>SO<sub>4</sub>).

With respect to claim 1, Formula III of Metzger does not contain an alkylating reagent having a haloketone or alpha haloaldehyde functional group said alkylating reagent having its haloketone or haloaldehyde functional group derivatized with a protected functional group. As stated in the claim the protected functional group renders the alkylating agent, when under biological conditions, unreactive to a nucleophilic or sulfhydryl group and reactive to a nucleophilic or sulfhydryl group, when under biological conditions, by action of an enzyme on the protected functional group. None of these features are disclosed or suggested by Metzger.

As discussed in the prior response, to the contrary and as is shown by Metzger, Formula III when in the presence of a nucleophilic group reacts with the nucleophilic group. It is unprotected and does not have the functional group used for alkylation derivatized with a protected functional group

as required by the present claims. For instance, in Formula II a nucleophilic group (a sulfhydryl) will form upon contact with a strong reducing agent such as the Zn/acid mixture. Upon forming the nucleophilic group from the compound of Formula II, the nucleophilic group reacts with the compound in Formula III to form the compound in Formula I. In complete contrast, substituting the composition of claim 1 for Formula III there would be no reaction with a nucleophilic group generated from Formula II from the action of the Zn/acid mixture because the compositions of claim 1 comprises an alkylating agent that comprises a "protected functional group" not found, disclosed, or even suggested by Metzger.

The same applies to the other claims. Even in the presence of a reducing agent such as the Zn/acid mixture the "protected functional group" remains protected. This is neither taught nor suggested by Metzger.

Thus, Applicants urge that the Examiner withdraw the rejection.

#### 102(b) Rejections under Van Atta

Claims 1, 14-16, 19, 21-30, 32, 33, and 27-44 stand rejected as being anticipated by Van Atta.

The Examiner states that Van Atta discloses compositions, kits and assays for performing immunodetection of homocysteine - both homogeneous and heterogeneous and that Van Atta discloses "modifying reagents, especially 'alkylating reagents' and preferentially BABA. The examiner states that BABA (e.g. example IV) and a modified BABA (e.g. BABA-N-hydroxysuccinamide ester at col. 21) are "protected alkylating agents" within the scope of the claimed invention. In addition the Examiner states that Van Atta also discloses "releasing agents" particularly "disulfide

reducing agents". Thus, the Examiner concludes that claims 1 and 14-16 which merely require a "protected alkylating reagent alone or further combined with a disulfide reducing agent" (e.g. TCEP). Applicants respectfully traverse the rejection.

Applicants claim a alkylating reagent, that is as currently recited: a composition comprising an alkylating reagent alkylating reagent having a haloketone or alpha haloaldehyde functional group said alkylating reagent having its haloketone or haloaldehyde functional group derivatized with a protected functional group. The protected functional group renders the alkylating agent, when under biological conditions, unreactive to a nucleophilic or sulfhydryl group and reactive to a nucleophilic or sulfhydryl group, when under biological conditions, by action of an enzyme on the protected functional group.

Van Atta does not disclose an alkylating reagent that has a protected functional group. Van Atta instead discloses the opposite. With reference to BABA: When BABA is in the presence of a nucleophilic group (e.g. reduced homocysteine) the BABA reacts with the free Hcy. See Van Atta at column 29, lines 60 to column 30, lines 35. Thus, BABA is not an alkylating reagent having the metes and bounds set out in Applicants' claims. It is not unreactive to a nucleophilic group when in the presence of such nucleophilic group. The same holds true for BABA-NHS. Van Atta at column 22, line 15 describes the reaction of BABA-NHS with BSA, which in the presence of DMSO forms BABA-activated BSA. In turn the BABA-activated BSA reacts with homocysteine. See column 22, lines 14-59. In contrast, a protected-BABA would not react with a nucleophilic group until the protected functional group was deprotected. Thus, Van Atta does not disclose or suggest the present invention.

Further, Applicants note that the use of alkaline phosphatase as discussed in Van Atta at col. 21-23 and throughout Van Atta has nothing to do with using alkaline phosphatase to "deprotect" a "protected" alkylating reagent as claimed by Applicants. Van Atta does not disclose alkylating reagents that have a protected functional group capable of reacting with a nucleophilic group when deprotected wherein the protected functional group is unreactive to a nucleophilic group when in the presence of a nucleophilic group. There is nothing the alkylating reagents disclosed in Van Atta that could be "deprotected" by alkaline phosphatase. Thus, Applicants respectfully request that the rejections under Van Atta be likewise withdrawn.

#### Nonstatutory Double Patenting Rejections under Van Atta

Claims 1, 14-16, 19, 21-30, 32, 33, and 27-44 stand rejected under the judicially created doctrine of double patenting over claims 1-29 of U.S. 5,478,729 (Van Atta). Applicants note that claim 46 has been cancelled.

Applicants submit that the claims are not obvious in view of Van Atta for the reasons discussed above. Van Atta neither discloses nor suggests the protected alkylating reagents defined by the claims as amended. In contrast to the present invention the alkylating reagents disclosed by Van Atta react with nucleophilic groups. Thus, Applicants respectfully request that the rejection be withdrawn.



If the Examiner believes that a telephone call to the undersigned would clarify any issue, Applicants respectfully invite the Examiner to contact Applicants attorney at the phone number given below.

Respectfully submitted,



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302/631-0360

Claims (Marked to show Changes)

Claim 1 (twice amended). A composition comprising an alkylating reagent having a haloketone or alpha haloaldehyde functional group said alkylating reagent having [a] its [protected] haloketone or alpha haloaldehyde functional group derivatized with [said] a protected functional group wherein said protected functional group renders the alkylating agent, when under biological conditions, unreactive to a nucleophilic or sulfhydryl group and reactive to a nucleophilic or sulfhydryl group, when under biological conditions, by action of an enzyme on the protected functional group [capable of reacting with a nucleophilic group when deprotected wherein the protected functional group is unreactive to a nucleophilic group when in the presence of a nucleophilic group].

Claim 19 (twice amended). A kit for use in a method for detecting and determining the amount of homocysteine in a sample, comprising in a packaged combination: a first reagent comprising an alkylating reagent having a haloketone or alpha haloaldehyde functional group, said haloketone or alpha haloaldehyde functional group derivatized with a protected functional group [having a protected functional group] said protected functional group capable of reacting with [a nucleophilic] the sulfhydryl group of homocysteine to form modified homocysteine when said protected functional group is deprotected, a second reagent comprising an activating reagent capable of deprotecting said [protected] alkylating reagent by removal of the protected functional group, and a third reagent capable of specifically binding to said modified homocysteine, each in an amount sufficient to conduct at least one assay.

Claim 32 (amended). A method of determining the amount of homocysteine in a sample suspected of containing said homocysteine, comprising the steps of:

- (c) bringing together in an aqueous medium:
  - (5) said sample,
  - (6) a first reagent comprising [a protected] an alkylating reagent having a haloketone or alpha haloaldehyde functional group, said haloketone or alpha haloaldehyde functional group derivatized with a protected functional group [having a protected functional group said protected functional group]\_capable of being activated to chemically modify the sulfhydryl groups of homocysteine to form modified homocysteine, and
  - (7) a second reagent comprising an antibody capable of specifically binding to said modified homocysteine to form an immunocomplex; and
  - (8) a third reagent capable of activating said protected alkylating reagent.
- (d) measuring the amount of said immunocomplex, the amount thereof being related to the amount of homocysteine in said sample.

Claim 44 (amended). A method of determining the amount of homocysteine in a sample, wherein at least a portion of said homocysteine is in the free disulfide form, comprising the steps of:

- (c) preparing an admixture comprising:
  - (6) said sample,

- (7) a releasing agent to release said homocysteine from the disulfide form,
  - (8) an alkylating reagent having a haloketone or alpha haloaldehyde functional group, said haloketone or alpha haloaldehyde functional group derivatized with a protected functional group [having a protected functional group said protected functional group] capable of being activated to chemically modify the sulfhydryl groups of homocysteine to form modified homocysteine, and
  - (9) an antibody capable of specifically binding to said modified homocysteine to form an immunocomplex, and
  - (10) an activating reagent capable of deprotecting said protected functional group of said alkylating reagent; and
- (d) examining said medium for the amount of said immunocomplex, the amount thereof being related to the amount of homocysteine in said sample.